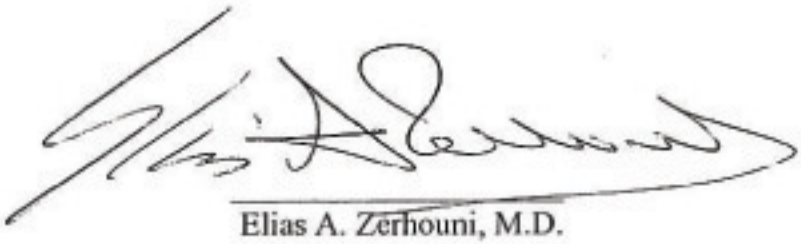
DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Neurological Disorders and Stroke

# PARKINSON'S DISEASE RESEARCH AGENDA



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**Executive Summary**

In Senate report No. 107-216 (pp. 153-154), the Senate Committee on Appropriations requests the National Institutes of Health (NIH) to devote additional resources to Parkinson's disease (PD) research using all available mechanisms, including Requests for Applications (RFAs) and further support of National Institute of Environmental Health Sciences (NIEHS) initiatives.

Over the past three years, NIH has devoted considerable resources to its implementation of the Parkinson's Disease Research Agenda. NIH Institutes and Centers involved in the implementation of the Agenda have built upon past commitments to this area of research and initiatives that were already in the planning stages at the time the Agenda was developed. This effort has led to the development of multiple centers of excellence, new grant applications on important topics, targeted contracts, consortia in several research areas, and research workshops. As a result of these many initiatives, numerous scientific advances have been made, the best new ideas have been funded, junior investigators and researchers from other disciplines have been encouraged to apply for grants on PD, and dozens of new studies – including important clinical trials – have been initiated.

In the last year alone, the ongoing implementation of the Agenda has been reflected in the continued commitment of the NIH to addressing emerging areas of research opportunity as rapidly as possible, while maintaining a solid base of meritorious investigator-initiated research, in the overall level of funding for PD research, and most important, in the science advances that have emerged from the field. Recent advances alone have included exciting developments in the treatment of PD in humans, as well as progress in gene therapy, the use of neurotrophic factors, and replacement cell therapy in animal models of the disease, and developments in imaging, environmental risk factors, and the cellular pathology of PD – just to name a few.

These advances are encouraging. However, NIH continues to look ahead to new challenges, and is already addressing many of the suggestions for an enhanced research focus identified at the January 2002 Parkinson's Disease Research Agenda implementation review consortium meeting. In addition, NIH also convened a scientific Summit meeting in July 2002 to review the status of PD research in the

United States and abroad, and to identify any "roadblocks" that may be slowing research in the field. The Summit was very successful in identifying roadblocks and NIH staff has drafted a matrix of short-to-long term, and low-to-high risk action items designed to target these issues.

NIH is committed to addressing these action items, both through enhanced support of individual Institute and Center efforts, and through improved coordination and collaboration with the research and voluntary PD communities.

## Introduction

In its report for the Fiscal Year 2003 appropriation for the Department of Health and Human Services (DHHS), the Senate Committee on Appropriations stated:

> "The Committee is aware that the Parkinson's Disease Research Agenda developed by the NIH in 2000 included professional judgment funding projections that totaled an additional $1,000,000,000 over 5 years. It is the clear intent of the Committee that the NIH, which has received substantial funding increases in recent years, come as close as possible to fulfilling that Agenda while maintaining the standards of peer review.
>
> The Committee was extremely disappointed, therefore, to learn that during fiscal years 2001 and 2002--the first 2 years of the Parkinson's Disease Research Agenda-NIH funding increases for Parkinson's failed to keep pace with funding increases for NIH overall. In addition, the NIH's projected Parkinson's budget for fiscal year 2003 falls $138,200,000 short of the $353,300,000 professional judgment budget estimate cited by the Agenda for that year. As a consequence, the NIH would fall even further behind on implementing the Agenda, and this highly promising field of research would not move ahead as speedily as the Congress intended.
>
> The Committee strongly urges the NIH to devote additional resources to Parkinson's research using all available mechanisms, including RFAs and further support of NIEHS initiatives.
>
> The Committee expects the NIH to report to Congress by April 1, 2003, on the steps it is taking to fulfill the Parkinson's Disease Research Agenda." (Senate Report No. 107-216, pages 153-154)

The following report has been prepared by the National Institutes of Health (NIH) of the DHHS in response to this request.

## Background

In FY2000, Congressional report language directed the NIH to develop a Parkinson's disease (PD) research agenda for the subsequent five years, including professional judgment budget estimates. At that time, NIH developed a broad

Agenda, based on input from leading academic researchers in the field, pharmaceutical experts, NIH staff, and several PD advocacy groups.

**Progress to Date on the Parkinson's Disease Research Agenda**

Since March of 2000, NIH has made considerable progress in implementing the scientific plan outlined in the PD Research Agenda. The National Institute of Neurological Disorders and Stroke (NINDS) has led these efforts, and its research is focused on many critical areas of the Agenda, including genetics, the cell biology of dopamine neurons/systems, the underlying pathology of PD, gene therapy, cell replacement therapies, drug development, translational research, and clinical trials. However, many other Institutes and Centers (ICs) have also been involved, including the:

National Institute on Aging (NIA): supports research on PD as part of a comprehensive program examining the causes and treatment of age-related neurodegenerative diseases (e.g., Alzheimer's disease, other dementias).
National Institute of Mental Health (NIMH): provides funding for research targeted to the cognitive and emotional effects of PD (e.g., depression, dementia), including the development of animal models of these effects.
National Institute of Environmental Health Sciences (NIEHS): provides support for research on environmental influences (e.g., natural or man-made toxicants) that may contribute to the development of PD, including the interactions between environmental agents and other factors (e.g., genes).
National Institute on Drug Abuse (NIDA): supports a strong program of research on the dopamine system, which plays a central role in the pathological cellular changes that lead to PD. NIDA areas of focus include the factors that cause the death of dopamine neurons, markers of these cells, and factors that modulate the entire dopamine system.
National Center for Research Resources (NCRR): provides support for critical research technologies, research infrastructure and facilities, and the sharing and distribution of clinical, animal, and biotechnology resources. NCRR supports PD-related protocols at General Clinical Research Centers (GCRCs), advanced neuroimaging through the Biomedical Informatics Research Network (BIRN), primate work at the National Primate Research Centers, and access to NIH-approved human embryonic stem cells.

National Institute on Deafness and Other Communication Disorders (NIDCD): supports research on the effects of PD on speech and related functions such as swallowing.
National Human Genome Research Institute (NHGRI): supports research on the genetic contributions to the development of PD, including the development and analysis of gene-based animal models of the disease.
National Institute of Child Health and Human Development (NICHD): supports research on human development and the maintenance of health, which currently includes research to examine how sensation is altered in individuals with PD.
National Center for Complementary and Alternative Medicine (NCCAM): provides support for the evaluation of complementary and alternative therapies in individuals with PD, as well as for core facilities in this area of research.
National Institute of Nursing Research (NINR): provides funding for research projects that are targeted to quality of life and care giving issues. Mobility disorders and chronic conditions like PD are often included in their grant solicitations.

In January 2002, NIH held a Parkinson's Disease Research Agenda implementation review consortium meeting at the request of Congress, and provided a full report on this meeting to the Committee in a March 2002 Congressional Appropriations Committee Report (CACR). This CACR also reported on grant solicitations and other NIH activities initiated through December 2001 that address the PD Research Agenda (see Appendix for an abbreviated list). In many areas of research, the participants agreed that NIH had taken an appropriate course of action and should continue its efforts. However, they also noted several research areas that warrant continued or increased attention in the coming years. These include:

- Facilitating translational approaches to PD research;
- Increasing our understanding of how PD effects the dopamine systems of the brain;
- Broadening studies of the effects of PD on cells and circuits other than dopamine systems, including treatment of non-motor complications;
- Improving and validating biomarkers and assessment tools;
- Supporting the necessary preclinical studies of gene therapy and facilitating translation into clinical trials;
- Supporting improvements in models of PD in invertebrates, small mammals and nonhuman primates.

In order to address these needs as rapidly as possible, NIH ICs developed a number of new initiatives, and reached significant milestones in other projects previously underway:

- NINDS released three general Program Announcements (PAs) in July 2002, to encourage applications on translational research in neurological disease. These PAs are designed to implement a program of cooperative agreements that will support milestone-driven projects focused on the identification and pre-clinical testing of new therapeutics, to recruit exploratory/developmental projects, and to enhance the Institute's support for the training of investigators in translational research.
- NINDS released a PA in July 2002 on the "Pathogenesis and Treatment of Dyskinesias in Parkinson's Disease." This PA, which includes set-aside money, is designed to support the study of the cellular basis of dopamine-induced dyskinesias and the study of non-dopaminergic drug therapies for the treatment of these dyskinesias.
- In May 2002, NINDS, NIA, NIMH and NIDCD released a PA to solicit applications on "Basic and Translational Research on the Cognitive Sequelae of Parkinson's Disease." The goal of this PA is to enhance research on the underlying neurobiological mechanisms associated with the cognitive and linguistic sequelae of PD.
- NIMH released a PA entitled "Research on Co-morbid Mental and Other Physical Disorders" in January 2002. This PA encourages studies of mental disorders that are co-morbid with other disorders such as PD. In October 2002, NIMH released a second PA entitled "Research on Mental Illnesses in Older Adults." This PA also fosters research into psychiatric disturbances that are co-morbid with medical illnesses, such as PD.
- NINDS is in the process of developing a workshop on the diagnosis of depression in PD to be held in Fall 2003.
- NINDS is in the process of developing a workshop on the diagnosis of depression in PD to be held in Fall 2003.
- NINDS awarded support (including monies from the NIH Director's Discretionary Fund) in September 2002, for a large translational study on gene therapy in PD. This project will be milestone-driven, and will involve extensive cooperation with, and funding management by, NINDS staff (see the "Program Highlights" section below for more information).

- In April 2002, NINDS announced the availability of "Administrative Supplements for the Sharing and Distribution of Mouse Genetic Models." These supplements are designed to support and encourage the timely sharing of mouse genetic models (or other rodent genetic lines) included within the scope of currently-funded NINDS research projects. One application was awarded specifically to promote the distribution of transgenic mouse PD models.
- NINDS and the Directors of the Udall Centers included a session on animal models of PD at their August 2002 meeting. This discussion focused on the variety of PD models that are available, the usefulness of these models in addressing critical research questions, and approaches NINDS can use to facilitate the sharing of these models as a research resource.
- NINDS is currently developing a website that will facilitate the sharing of information on animal models of PD throughout the research community, as well as enhance the exchange of the models themselves.

NIH ICs have also made significant progress in advancing many other important areas of the PD Research Agenda since January 2002. Some examples are outlined below:

- In May 2002, the Steering Committee for the NINDS Parkinson's Disease Neuroprotection Trial selected a panel of drug therapies to be tested in the pilot phase of this trial. The Committee considered a set of compounds that had been evaluated previously and ranked based on a series of stringent criteria (see the "Program Highlights" section below for more information).
- In May 2002, NINDS and the Department of Veterans Affairs (VA) signed a Memorandum of Understanding to conduct the largest trial of deep brain stimulation (DBS) for PD to date. This trial will enroll 300 subjects at both VA and affiliated academic research sites, and will compare DBS to best medical management in its initial phase, and in a subsequent phase, will compare the effectiveness of DBS at two different brain sites.
- In August 2002, NIEHS announced awards for three Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER). These Centers will utilize the funds provided under this program to bridge their ongoing NIH-supported work in environmental causation of PD (see the "Program Highlights" section below for more information).

- In September 2002, NINDS awarded a contract to the Coriell Institute to develop a "DNA Repository for Human Genetics." This repository of data, cell lines, and DNA samples, will be designed to enhance the study of the genetic factors contributing to neurological diseases, and PD is one of three diseases to be included in the "ground floor" development of this resource. As of January 2003, Coriell had already archived samples from over 60 individuals with PD as part of this contract.
- In October 2002, NINDS released a PA to solicit applications for new and existing PD research centers to compete for "Morris K. Udall Parkinson's Disease Research Centers of Excellence" awards; NIEHS is a co-sponsor of this announcement. This PA is a key step to facilitate the continuation of the Udall Centers program, within the context of the NIH merit-based review process.
- In November 2002, the NIEHS provided support for the Twentieth International Neurotoxicology Conference, entitled "Emerging Issues in Neurotoxicology," held in Little Rock, Arkansas. PD was one of the featured topics of this conference. Two scientific sessions highlighted current research in environmental risk factors and the creation of new research paradigms to address gene-environment interactions in disease initiation and progression.
- In December 2002, NIA released an RFA entitled "Collaborative Studies on Alzheimer's Disease and Other Neurodegenerative Diseases Associated with Aging"; NINDS is a co-sponsor of the RFA. The purpose of this RFA is to facilitate collaborative cross-disciplinary and multi-institutional approaches that will contribute new and vital information about the clinical and pathological course of normal aging and the neurodegenerative diseases associated with aging, including PD.

*Program Highlights*

Although NIH has many projects and programs underway that are directly or indirectly contributing to progress in PD research, several of these activities are of particular importance in the overall efforts to implement the PD Research Agenda. Examples are highlighted below:

Gene Therapy for Parkinson's Disease

As part of its efforts to enhance translational research in PD, NINDS has recently awarded a grant for a large, multi-center, multidisciplinary, preclinical investigation

of both dopaminergic enzyme gene therapy and neurotrophic gene therapy in non-human primate models of PD. Goals of the project will include comparison of the different genes, and the testing of different gene delivery approaches. Investigators will also evaluate the safety, toxicity, efficacy, and longevity of these delivery vehicles, as well as their ability to turn gene expression on or off as needed. The program will include administrative and statistical cores, and a special project devoted to development of bioethics principles for gene therapy in individuals with PD. The overall study is unique in that it is milestone-driven, and will function as a cooperative agreement with participation from NINDS program staff to set milestones and assess progress. A Steering Committee composed of the investigators in the trial and NINDS staff will make decisions regarding which genes and vectors will continue to be pursued based on discoveries and results. This group will report periodically to a larger Advisory Committee that will include external scientific advisors and members of the lay community; this committee will help guide the project by monitoring achievement of the proposed milestones.

NIH anticipates that by supporting a rational, coordinated and integrated approach to the development of gene therapy treatments for PD, researchers can achieve the ultimate goal of laying the groundwork necessary for an Investigational New Drug application to the U.S. Food and Drug Administration necessary to proceed to clinical trials in humans.

Parkinson's Disease Neuroprotection Trial

Treatments that are currently used for PD are useful in reducing the impact of most individuals' symptoms, but these therapies become less effective over time, as the underlying disease progresses. For this reason, the identification of therapies that can slow or stop the progression of PD would be of tremendous benefit. To address this goal, NINDS has committed to a series of studies to evaluate potential neuroprotective agents in treating PD. A team of pharmacologists, clinicians, and clinical trial experts – including NINDS staff – developed specific criteria for the evaluation of potential therapies, including scientific rationale, blood-brain barrier penetration, safety and tolerability, and evidence of efficacy in animal models or humans. The team of reviewers solicited suggestions from scientists and clinicians in academia and industry, as well as patient and foundation groups, in order to identify as many potential therapies as possible. A Steering Committee for this trial has since selected a small number of compounds to be evaluated in pilot studies –

the first of which may be initiated as early as the spring of 2003. Agents that prove successful in the pilot phase will be evaluated in larger Phase III trials.

Collaborative Centers for Parkinson's Disease Environmental Research Program:

In response to the accumulating evidence for significant environmental influences in PD, and the likely role of gene-environment interactions in disease etiology, NIEHS developed and launched a major new research initiative in 2002, the Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) Program. This Program seeks to strengthen the integrative collaboration among NIH-funded scientists engaged in fundamental laboratory research in PD and geneticists, clinicians and epidemiologists, allowing leads uncovered in one area to be pursued quickly in others.

The centerpiece of the CCPDER Program is a highly interactive national network of three research Centers that function to share data and resources and to engage in the planning and conduct of collaborative studies relevant to environmental factor causation in PD. In addition to its role in the larger network, each CCPDER is engaged in a separate NIH-funded program of research activities that focus on gene-environment interactions in PD. For example, two of these Centers also receive funding from NINDS as part of the Institute's Udall Centers program. An essential component of the CCPDER Program is active involvement of the lay PD community. This is achieved in several ways, including participation of lay representatives as members of External Advisory Boards of each CCPDER, and through planned collaborative design and evaluation of a CCPDER website that facilitates information exchange with the PD scientific and lay communities.

Deep Brain Stimulation Consortium

The NIH Deep Brain Stimulation (DBS) Consortium is a core group of researchers funded under an NINDS/NIA-sponsored RFA to explore DBS and its therapeutic applications from several different disciplinary perspectives. This RFA specified that an annual workshop/meeting among grantees and other interested members of the DBS community should be organized to develop collaborations among members of the consortium and an enhanced sense of community among DBS researchers and practitioners.

The first of these annual meetings took place on in Rockville, MD in June 2002, and brought together an international gathering of physicians, basic scientists, patient advocates, industry representatives, and governmental officials to discuss

issues surrounding the use, technology, mechanisms, and ethics of DBS. Representatives from nine of the eleven DBS Consortium member institutions currently funded by the NIH presented their work at the meeting. Since the formation of the initial consortium group, two additional RFAs have been released by the NIH (one by NINDS, the other by NINDS/NIMH), and it is anticipated that the investigators funded under these solicitations will be involved in future consortium activities.

PET Scanning in Parkinson's Disease

Some of the families enrolled in NIH intramural projects designed to identify the genes that are associated with PD do not have a sufficient number of clearly-affected individuals to perform the intended studies. Therefore, NHGRI has collaborated with researchers from NINDS, NIMH and the NIH Clinical Center to perform PET scans on family members who may or may not be affected by PD, in an effort to further clarify their risk for developing the disease. Researchers are comparing the brain's use of dopa in individuals with PD, their family members, and normal volunteers. Dopa is the precursor of dopamine and is a chemical normally found in the part of the brain involved in controlling movement. In people with PD, the cells that convert dopa to dopamine begin to die, and by the time that symptoms of PD begin, they are only producing 20-30 percent of the normal levels of dopamine. Thus, the use of PET scans in these potentially affected family members may help to classify them based on the number of cells they have that can take up dopa for conversion to dopamine. A better classification of these subjects using this approach may aid researchers in identifying individuals who would be appropriate for further genetic studies.

*Recent Scientific Advances*

In 2002, NIH-funded scientists published a number of important advances in PD research. A few examples of these advances are described below:

Promising Results from Coenzyme Q10 Study

Recent results from a NINDS-funded, placebo-controlled clinical trial suggest that the antioxidant Coenzyme Q10 (CoQ) may slow the progression of PD symptoms, when used at higher doses than have been evaluated previously in neurological disorders. Eighty subjects with early PD participated in this study, which compared the progression of functional loss in subjects receiving CoQ at three different doses to the progression in subjects receiving an identical placebo. Over the course of the

16-month followup, subjects receiving the highest dose of CoQ exhibited the largest preservation of function. In the past, trials of CoQ for neurological disorders have not clearly indicated an effect of the compound in slowing symptom progression. However, these data suggest that higher doses may need to be evaluated in future studies in order to maximize the potential treatment effects.

Positive Effects of a Neurotrophic Factor in an Animal Model of PD

Scientists have known for many years that the glial cell line-derived neurotrophic factor (GDNF) can have profound effects on the survival and outgrowth of some types of dopamine neurons. In a recent study supported by NINDS, NIA and NIMH, researchers demonstrated that the direct infusion of GDNF into a region of the brain compromised in PD can have profound effects on monkeys that are in an advanced stage of parkinsonism. The GDNF, delivered chronically via an implanted pump, both improved motor function and restored several aspects of the dopamine system in these animals, suggesting that it may be a promising compound to evaluate further as a treatment for PD in humans.

Activity Patterning and PD Tremors

One of the hallmarks of PD is the development of tremors, but until recently, researchers did not understand how a depletion in brain dopamine could lead to this motor abnormality. However, recent NINDS-funded research has demonstrated, through mathematical modeling, that specific circuits in the brain regions affected by PD can produce several different patterns of neural activity. These findings shed new light on the biological mechanisms that might be involved in the generation of rhythmic movements in individuals with PD. Results such as these may also lead to the development of more realistic stimulation patterns for deep brain stimulation.

Gene Therapy

Several different approaches to gene therapy – including a variety of delivery vehicles and agents to be delivered – have been considered in attempts to reverse the neurological deficits in animal models of parkinsonism. Delivery of the enzyme that helps to synthesize L-dopa, a precursor of dopamine, is one such approach, although in the past it provided only limited benefit in reversing parkinsonian deficits in rats. However, a recent NINDS-funded study in a rodent model suggests that this approach can provide long-lasting reductions in parkinsonian behaviors, if the enzyme responsible for producing a necessary co-factor (GTP) is also delivered

via gene transfer. Using this combined technique, investigators were able to identify the minimal tissue level of tissue L-dopa necessary to achieve the effects they observed.

Stem Cell Transplantation

NINDS intramural researchers have recently obtained encouraging results with mouse embryonic stem cells, demonstrating that by driving a specific pathway of gene expression and applying other specific chemical signals, these cells can be influenced to develop into dopaminergic neurons in culture. These cells in turn can be transplanted into a rodent model of PD, where they appear to survive, integrate with the host tissue, and reverse some motor impairments.

Other NINDS-funded researchers have also obtained similar results by transplanting low doses of mouse embryonic stem cells into an area of the rat brain that has been implicated in PD. They found that these cells could successfully develop into dopaminergic neurons, integrate with the host tissue, and reverse asymmetric motor deficits characteristic in at least one type of rodent PD model. The use of low doses of cells was believed to play an important role in the ability of the cells to develop into neurons. It is important to note that some transplanted cells grew into uncontrolled tumors, illustrating the need for more research before embryonic stem cell transplantation clinical trials are considered in humans.

Comparison of Effects of Levodopa and Deep Brain Stimulation

Impairment of postural control is a major problem in patients with PD. Researchers supported with NIA funding (under the DBS RFA) have compared the relative effects of pharmacological treatment and DBS on the stability of individuals with PD when they are standing at rest. Their results indicated that treatment with levodopa actually increased postural sway abnormalities, whereas treatment with DBS improved postural control. Evaluation of postural stability may be a useful addition to the standard clinical testing of patients with PD, and may help in risk assessment for falls in PD patients.

Automated Labeling of Neuroanatomical Structures in the Human Brain

Neurodegenerative disorders, psychiatric disorders, and healthy aging are all frequently associated with structural changes in the brain. Rapid and accurate techniques exist for assessing variability in the cerebral cortex, the outermost portion of the brain. However, the current method for detecting changes in regions below the cortex, or subcortical regions, requires manual labeling, which

can take up to a week for high-resolution images. NCRR and NINDS-funded researchers have recently developed a new technique for automatically assigning a neuroanatomical label to each 3-D point, or voxel, in a brain image produced through magnetic resonance imaging (MRI). The automated procedure takes approximately 30 minutes. In addition, multiple processes can be run in parallel, enabling the labeling of thousands of brain images per day, which can be a major asset for clinical evaluation of neurological disorders and normal aging.

Selective Death of Dopamine Neurons by the Herbicide Paraquat

A number of epidemiological studies have suggested an association between exposure to pesticides and increased risk of PD. Paraquat is the pesticide that has been implicated most often. In a recent study supported by the NIEHS, researchers demonstrated that systemic exposure of mice to paraquat reproduced one of the hallmark features of PD, selective degeneration of the neurons that form one of the critical dopamine pathways in the brain. This loss of cells occurred despite the maintenance of normal dopamine levels in the target brain region, which suggests that other surviving neurons may compensate for the toxicant-induced damage by producing additional dopamine. This study supports the role of pesticides as a risk factor for PD, and the use of paraquat exposure in rodents as a potential model to study PD. In addition, these results also suggest that neurotoxicant-induced injury may remain 'silent,' due to compensation by surviving cells, and that additional environmental and/or genetic risk factors may be needed for full-blown parkinsonian changes to occur.

The Interaction of Genetic and Environmental PD Risk Factors in Men and Women

The most difficult challenges in identifying the cause(s) of sporadic PD include establishing the environmental, occupational and lifestyle exposures that confer risk, identifying genetic factors that most often modify such risk, and determining the relative roles that each of these factors, alone and interactively, plays in disease causation. Two important issues concerning genetic risk factors are the difficulty of confirming associations of many candidate genes with PD and, sometimes, the lack of substantial effects from a particular gene mutation. Although a number of factors contribute to these difficulties, it is likely that the presence of complex interactions among risk factors is a particularly significant contributor. An illuminating example of the complex relationships that may exist was reported recently in an NIEHS-supported study. This researcher found the presence of an

interaction between gender, smoking, and the presence of a change in the gene that codes for monoamine oxidase A (MAO-A), a protein involved in the breakdown of dopamine. In men, a protective effect of smoking (demonstrated in previous research) was present only in individuals with one particular change to the MAO-A gene. By contrast, this genetic change did not alter the protective effect of smoking in women.

Role of Zinc in Dopamine Transport

Dopamine transporters regulate the ratio of dopamine outside the cell to concentrations of dopamine inside the cell. Inward transport requires binding of dopamine at the surface of the neuron, transport across the cell membrane, and release inside the neuron. This process is deficient in individuals with PD, largely because neurons expressing the dopamine transporter degenerate. Transport of dopamine and the transporter itself are also of considerable interest in drug abuse research because some abused drugs, such as amphetamine, can use the transporter to enter the neuron, where they can be toxic. NIDA-supported researchers have identified an area of the transporter molecules that prevents dopamine transport at high concentrations. The binding site is regulated by zinc, which stabilizes the changes to the transporter that enable movement of dopamine to occur. This site may provide researchers with a potential target in the design of medications that may alleviate the symptoms of PD, as well as treating problems associated with drug addiction.

The Role of Iron in PD

Multiple studies have implicated iron in the cellular changes that lead to PD, as well as other neurodegenerative disorders. Iron levels are elevated in the brains of patients with PD, and the levels of iron-binding proteins are abnormal. Although excess iron could damage neurons through several mechanisms, recent studies suggest that it may contribute to the development of PD by facilitating the accumulation of a protein called alpha-synuclein into cellular structures called Lewy bodies, which are a characteristic feature of PD. Researchers at NHGRI have found that the the levels of iron can affect the binding of alpha-synuclein proteins, and the data to date suggest a mechanism by which iron may be contributing to synuclein accumulation.

*Coordination and Collaboration*

NIH continues to coordinate the efforts of its ICs through regular meetings of the Parkinson's Disease Coordinating Committee (PDCC). NIH invites representatives of both the VA and the Department of Defense to participate in these meetings as well. Similarly, NIH has coordinated its efforts with the PD voluntary community through past meetings of the Parkinson's Disease Implementation Committee. More recently, this meeting has been supplanted by larger workshops including outside scientists, such as the PD consortium meeting held in January 2002, and regular conference calls involving representatives of the PD voluntary community and NIH staff to discuss issues of mutual interest (for example, recruitment for clinical trials and an international PD meeting).

## Continued Implementation and Future Planning

In addition to the January 2002 meeting, NIH also held a Coordination Summit with members of the scientific community in July 2002. The purpose of this Summit was to consider the global status of PD research, and to identify any roadblocks that might be impeding progress in the field. The Summit was very effective in identifying some of the roadblocks that are impacting PD research. Following the meeting, NIH staff developed a matrix of short-to-long term and low-to-high risk action items appropriate for the entire PD community to address. NIH has already forwarded a draft of the matrix to the Committee. Currently, the NIH and several private PD funding organizations have specific leadership responsibilities assigned in the matrix. However, it is anticipated that partners in other federal agencies and international supporters of PD research will collaborate with NIH in this effort in the future. Summit participants also reviewed information available at the time on the global research portfolio in PD; however, this process is still ongoing as information is still being received from other countries.

## Conclusions

NIH has been, and continues to be, strongly committed to the implementation of the scientific research defined in the PD Research Agenda. The extramural

scientific community has indicated that the scientific efforts made by NIH to date in PD research have been beneficial to the field, although work remains to be done. NIH will explore all possible avenues to accelerating progress on these topics, including support for initiatives by NINDS, NIEHS and other ICs, as appropriate. In addition, the research community has identified several roadblocks to research, as outlined in the matrix, that need to be addressed. Improved coordination of research at many levels – including better coordination of centers, resource sharing, and brain banking – is necessary, as is an enhanced role for the private PD organizations in activities such as patient education and outreach. NIH considers all of these issues of paramount importance in continuing the implementation of the PD Research Agenda, and will continue to devote the staff time and other resources needed to address these issues.

**Appendix**

**Implementation of the Parkinson's Disease Research Agenda through December 2001:**

*Grant Solicitations and Contracts*

- "Function of Synaptic Proteins in Synaptic Loss and Neurodegeneration" (March 2000, NINDS)
- "Mitochondrial Function and Neurodegeneration" (March 2000, NINDS, NIEHS)
- "Role of Parkin and Related Proteins in Parkinson's Disease" (April 2000, NINDS)
- "Self-Management Strategies Across Chronic Diseases" (June 2000, NINR, NHLBI, NIA, NIAMS, NICHD, NIDDK, NIMH, NINDS)
- "Stem Cell Plasticity in Hematopoetic and Non-hematopoetic Tissue," (November 2000, NHLBI, NIDDK, NINDS)
- "Gene Discovery for Neurological and Neurobehavioral Disorders" (March 2001, NINDS, NIA, NIMH)
- "Parkinson's Disease Neuroprotection Trial - Coordinating And Statistical Centers," (March 2001, NINDS) and "Parkinson's Disease Neuroprotection Trial - Clinical Centers," (July 2001, NINDS)
- "The Biology of Non-Human Stem Cells in the Environment of the Nervous System," (April 2001, NINDS, NIMH, NIDCD, NIA, NICHD); "Plasticity of Human Stem Cells in the Nervous System," (December 2001, NINDS, NIA, NIMH, NHLBI)
- "R21 Fast Track Grants for Parkinson's Disease Research" - (May 2001, NINDS, NIDCD, NIEHS, NIMH, Fox Foundation, Parkinson's Disease Foundation/National Parkinson's Foundation, Parkinson's Alliance)
- "Research on Research Integrity," (August 2000, re-released May 2001, Department of Health and Human Services (DHHS) Office of Research Integrity (ORI), NINDS)
- "Technology Development for Safe and Effective Deep Brain Stimulation" (July 2001, NINDS)
- "Mechanisms of Action of Deep Brain Stimulation" (July 2001, NINDS,

NIMH)
- "Gene Therapy for Neurological Disorders" (July 2001, NINDS, NICHD, NIA, NIDDK, NIDCD)
- "High Throughput Drug Screening Facility for Neurodegenerative Disease" contract (October 2001, NINDS)
- "Collaborative Centers for Parkinson's Disease Environmental Research," (December 2001, NIEHS)
- "Neurodegeneration Disease Assays for High Throughput Drug Screening and Chemical Genetics," (December 2001, NINDS)

*Supplements*

- "NINDS Administrative Supplements for Research on Parkinson's Disease" (November 2000, NINDS)
- "NINDS Administrative Supplements: FDA-approved Compound Screens for Neurodegeneration," (May 2001, NINDS)

Additional supplements awarded to individual investigators:
- To make microarray technology more readily available to researchers
- To start a brain-banking initiative
- To accelerate the study of PD in genetically isolated populations, and in racial minority and ethnic groups
- To develop high-throughput assays
- To develop and maintain a website devoted to sharing of biological reagents relevant to PD
- To permit laboratories with ongoing Parkinson's research grants to purchase equipment that will enhance their research programs

*Workshops/Meetings*

- "Parkinson's Disease Epidemiology Workshop," (September 2000, NIEHS)
- "Workshop on Therapeutic Opportunities in PD" (October 2000, NINDS)
- "Gene Therapy for Neurological Disorders" (October 2000, NINDS, ORD)
- Teaching workshop on the neurobiology of Parkinson's disease at the Society for Neuroscience meeting (November 2000, NINDS).
- "Cognitive and Emotional Aspects of Parkinson's Disease" workshop (January 2001, NINDS, NIA, NIMH)

- "Depression: The Unwanted Cotraveler - A Day for the Public." (March 2001, NIMH)
- "The Role of the Environment in Parkinson's Disease" (March 2001, NIEHS)
- "Synuclein and Cortical Lewy Bodies Associated with Dementia in AD, LBD, and PD," (July 2001, NIA, NINDS)
- "19th International Neurotoxicology Conference: Parkinson's Disease, Environment and Genes" (August 2001, NIEHS, co-sponsored by NINDS)
- "NIEHS Brainstorming Session on Parkinson's Disease" in conjunction with the 19th International Neurotoxicology Meeting (August 2001, NIEHS).